REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Claims 6 and 22-29 have been deleted without prejudice or disclaimer. Claim 21 has been amended to recite that the chronic heart failure is treated by "reducing pulmonary congestion not based on diuretic and hypotensive effects." Support for this amendment may be found at the very least at page 9, lines 18-21. No new matter is added by this amendment. Claim 8 was also amended to depend from claim 21.

Claims 26 and 27 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. This rejection is now moot in view of the deletion of these claims.

Claims 6, 8-11, and 21-29 are rejected under §112, first paragraph, as not being enabled. This rejection, as it applies to the claims now of record, is respectfully traversed.

More specifically, it is asserted that (1) treatment of species other than rats, (2) treatment with agents other than ANF, and (3) treatment in any species with any agents at plasma levels as claimed in claims 22, 24 or 26, or at a dosage as in claim 26, would not be enabled. This assertion with respect to (1) and (2) is believed to be in error. With respect to (3), this is rendered moot by the deletion of these claims.

As acknowledged in the Official Action, the specification shows treatment with ANF in rats. This showing is sufficient to enable the full scope of the claims. The references cited in

the prior art rejection show that this animal model is sufficient to enable the full scope of the claims. For example, in Blaine, at column 3, lines 11-16, it states that the peptides are useful to "treat disorders of electrolyte balance and/or altered vascular resistance in mammalian species, e.g., hamsters, mice and rats." Treatment in rats is shown. The claims cover treating of "a mammalian species." Blaine thus shows that "rats" were considered a representative, model species at the time of the invention, and the rat data would be enabling to a person skilled in the art for treatment of other subjects, including mammals an in particular humans.

Similarly, Espiner cites rat studies at, for example, page 206, 2nd column, 2nd paragraph, and page 207, 2nd column, 2nd paragraph. Rat and mice studies are also cited at page 207, 2nd column, 3rd paragraph - page 208. In discussing mice studies, Espiner states that "[s]imilarities to human disease, including essential hypertension, are obvious and raise the possibility that gene polymorphism (*eg*, in NPR-A) may underlie some forms of hypertension and sudden death in humans. Results from other transgenic models (*eg*, BNP knockouts, disruption of NPR-B and NPR-C, or combinations of these) are now eagerly awaited." Page 208, 1st column, last paragraph. References cited by Espiner further shows that mice and rat models were well recognized and accepted in the art. *See*, Table 1, page 208, and References 44-48 cited therein (Oliver et al, "Hypertension, cardiac hypertrophy, and sudden death in mice lacking natriuretic peptide receptor A," *PNAS* 1997, 94:14730-735; Steinhelper, "Hypotension in transgenic mice expressing atrial natriuretic factor fusion genes, *Hypertension*

1990, 16:301-07; Ogawa et al, "Molecular cloning of the complementary DNA and gene that encode mouse brain natriuretic peptide and generation of transgenic mice that overexpress the brain natriuretic peptide gene," *J. Clin Invest* 1994, 93:1911-21; John et al, "Genetic decreases in atrial natriuretic peptide and salt-sensitive hypertension," *Science* 1995, 267:679-81; Lopez et al, "Salt-resistant hypertension in mice lacking the guanylyl cyclase-A receptor for atrial natriuretic peptide," *Nature* 1995, 378:65-68). *See also,* Reference 36 (Endlich et al, "Natriuretic peptide receptors mediate different responses in rat renal microvessels," *Kidney Int.* 1997, 52:202-07) and Reference 43 (Wu et al, "Atrial natriuretic peptide induces apoptosis in neonatal rat cardiac myocytes," *J. Biol. Chem.* 1997, 272:14860-866).

Additional art cited during prosecution of this application further shows that the rat is a well accepted model in this art. *See, for example,* Brown et al, "Differential Regulation of Natriuretic Peptide Receptor Messenger RNAs during the Development of Cardiac Hypertrophy in the Rat," *J. Clin. Invest*, 1993, 92:2702-12; Cao et al, "Natriuretic Peptides Inhibit DNA Synthesis in Cardiac Fibroblasts," *Hypertension*, 1995, 25(2):227-34; Lin et al, "Cicletanine Inhibits Endothelin-1-Induced Hypertrophy of Rat Cardiomyocytes," 1996. 51(1):1-6.

In view of the above, it is respectfully believed that the rat data in the specification would be fully enabling to one skilled in the art of the full scope of the claims. Species such as rat and mouse were recognized as being appropriate models.

With respect to (2), the scope of the claims is also fully enabled. One skilled in the art could readily identify substances in addition to ANF that act on guanylyl cyclase A natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate. One skilled in the art could also test such substances to determine whether and at what dosage pulmonary congestion is reduced in order to treat chronic heart failure as instantly claimed, without a diuretic or hypotensive effect. One skilled in the art could follow the teachings of the instant specification, for example, at pages 11-12, and Example 3, at pages 18-20. No undue experimentation would be necessary for a person skilled in the art to follow these teachings using additional active agents which act on guanylyl cyclase A natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate. Such experimentation would not be "undue."

Claims 6, 8, 9, 21, 23 and 25 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Blaine et al as evidenced by Espiner. This rejection is respectfully traversed, as it applies to the claims now of record.

Neither Blaine nor Espiner teach or suggest that ANP would reduce pulmonary congestion and thus treat chronic heart failure as instantly claimed. There is no mention or recognition that a compound which will act on guanylyl cyclase A natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate will reduce pulmonary congestion and thus treat chronic heart failure. Instead, Blaine describes that ANP was administered for one week to unidentified rat models of cardiac hypertrophy and normal rats,

and the water content of the heart (grams H_2O/100 grams tissue) was determined. It describes that ANP inhibited hypertrophy, but indicated only a "reduction in water content." This teaching is unrelated to reduction of pulmonary congestion to treat chronic heart failure, as instantly claimed.

Espiner is a review of "recent work that has increased our knowledge of hormone secretion, metabolism, local actions, and physiologic significance. The reference fails to evidence knowledge in the art at the time of the invention of "treatment of chronic heart failure by reducing pulmonary congestion not based on diuretic and hypotensive effects," as instantly claimed.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

Claims 6, 8, 9, 21, 23 and 25 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine in view of Cao et al. This rejection is respectfully traversed, as it applies to the claims now of record.

Neither Blaine nor Cao et al teach or suggest that ANP would reduce pulmonary congestion and thus treat chronic heart failure as instantly claimed. There is no mention or recognition that a compound which will act on guanylyl cyclase A natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate will reduce pulmonary congestion and thus treat chronic heart failure. As stated *supra*, Blaine describes that ANP was administered for one week to unidentified rat models of cardiac hypertrophy and normal

rats, and the water content of the heart (grams H_2O/100 grams tissue) was determined. It describes that ANP inhibited hypertrophy, but indicated only a "reduction in water content." This teaching is unrelated to the instantly claimed treatment of heart failure by reducing pulmonary congestion.

With respect to Cao et al, it similarly is unrelated to treatment of heart failure by reducing pulmonary congestion. Moreover Cao et al shows that use of ANP at 10^{-6} M has an inhibitory effect on the growth of about 30% of cardiac fibroblasts. This level is more than 1,000 fold of the blood level of ANP in applicants' method.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

Claim 10 has been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine in view of Espiner. This rejection is respectfully traversed.

Neither Blaine nor Espiner teach or suggest that ANP would reduce pulmonary congestion and thus treat chronic heart failure as instantly claimed. Neither Blaine nor Cao et al teach or suggest that ANP would reduce pulmonary congestion and thus treat chronic heart failure as instantly claimed. There is no mention or recognition that a compound which will act on guanylyl cyclase A natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate will reduce pulmonary congestion and thus treat chronic heart failure. As stated *supra*, Blaine describes that ANP was administered for one week to unidentified rat models of cardiac hypertrophy and normal rats, and the water content of the

heart (grams H_2O/100 grams tissue) was determined. It describes that ANP inhibited hypertrophy, but indicated only a "reduction in water content." This teaching is unrelated to the instantly claimed treatment of heart failure by reducing pulmonary congestion.

Espiner is a review of "recent work that has increased our knowledge of hormone secretion, metabolism, local actions, and physiologic significance. The reference fails to evidence knowledge in the art at the time of the invention of "treatment of chronic heart failure by reducing pulmonary congestion not based on diuretic and hypotensive effects," as instantly claimed.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

Claims 11, 28 and 29 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine. This rejection, as it applies to claim 11 now of record, is respectfully traversed.

Blaine fails to teach or suggest that ANP would reduce pulmonary congestion and thus treat chronic heart failure as instantly claimed. Blaine fails to teach or suggest that ANP would reduce pulmonary congestion and thus treat chronic heart failure as instantly claimed. There is no mention or recognition that a compound which will act on guanylyl cyclase A natriuretic peptide receptor and accelerate production of cyclic guanosine monophosphate will reduce pulmonary congestion and thus treat chronic heart failure. As stated *supra*, Blaine describes that ANP was administered for one week to unidentified rat models of cardiac

hypertrophy and normal rats, and the water content of the heart (grams H_2O/100 grams tissue) was determined. It describes that ANP inhibited hypertrophy, but indicated only a "reduction in water content." This teaching is unrelated to the instantly claimed treatment of heart failure by reducing pulmonary congestion.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

In view of the above, it is respectfully submitted that none of the cited references either alone or in combination disclose or suggest applicants' claimed methods. Withdrawal of the rejections of record, as they apply to the claims now of record, are respectfully requested and believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (508) 339-3684 so that prosecution of the application may be expedited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to Examiner Borin (Fax No. (703) 305-3014 at the U.S. Patent and Trademark Office on April 9, 2003.

4/9/03
Date

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Donna M. Meuth

Attachment to Reply and Amendment dated April 9, 2003

Marked-up Claims 8 and 21

8. (Twice Amended) A method as set forth in claim [6] 21, wherein the substance that acts on guanylyl cyclase A natriuretic peptide receptor and [is able to accelerate] accelerates production of cyclic guanosine monophosphate is a natriuretic peptide.

21. (Amended) A method for treatment of chronic heart failure by reducing pulmonary congestion [heart weight] not based on diuretic and hypotensive effects comprising [continuously] administering a substance that acts on guanylyl cyclase A natriuretic peptide receptor and [is able to accelerate] accelerates production of cyclic guanosine monophosphate to a subject in need of such treatment in an amount effective for reducing pulmonary congestion, wherein said amount does not produce [heart weight and not effective for said] diuretic and hypotensive effects.